

## **REMARKS/ARGUMENTS**

### **I. Status of the Claims**

Claims 1, 2, 6-12, 14-17, and 26-36 are pending. Claims 3-5, 13, and 18-25 have been canceled and claims 35 and 36 have been added herein.

### **II. The Present Amendments**

The amendments herein do not add new matter. The amendments to claims 1, 12, 15, and 26 recite that the platelets are resting. This recitation is supported throughout the specification, including page 11, lines 8-14. Claims 1, 12 and 26 have further been amended to recite that the platelets are able to respond to thrombin by clot formation within about three minutes at 37° C. This recitation is supported throughout the specification, including claim 13 as originally presented and page 4, lines 6-8.

The amendment to claim 7 clarifies the temperature range at which the platelets are loaded, and is supported throughout the specification, including page 8, lines 24-26. New claims 35 and 36 recite more preferred temperatures for loading and are supported by, for example, the same passage.

The amendment to claim 12 incorporates into claim 12 the functional recitation of claim 13, which has accordingly been canceled. The claim has also been amended to clarify the circumstances under which the biological properties are to be preserved. The recitation is supported throughout the specification, including page 8, lines 3-5.

### **III. The Office Action and Response Thereto**

The Action rejects the claims on several grounds. Applicants amend in part and traverse the rejections.

#### **A. Provisional double-patenting rejection**

Claims 1-17 and 26-34 are provisionally rejected for obviousness-type double patenting over claims 51-52 of copending application 10/807,614. As the Examiner correctly

notes, the allegedly conflicting claims have not in fact been patented. Accordingly, it is requested that this rejection be held in abeyance until the claims in one of the applications are indicated to be allowable.

#### **B. Rejection for indefiniteness**

Claims 1-17 and 26-34 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for reciting the phrase "a normal response to at least one agonist." According to the Action, the metes and bounds of this recitation are unclear and this renders the claims indefinite. The Action then cites a number of cases for the proposition that the language of the claim must make it clear what the claim encompasses.

For the sake of good order, Applicants note that the rejection is incorrectly applied to claim 13, which recites a specific response to a specific agonist. Applicants further respectfully note that the rejection does not seem to apply to claims 26-34, since claim 26 does not contain the recitation objected to by the Action. Applicants are left to surmise that the Action intends to apply the indefiniteness rejection to the recitation in claim 26 to preserving biological properties. Applicants further maintain that claims 1-10 and 15-17 as originally presented are clear to persons of skill in the art.

To expedite prosecution, however, claims 1 and 15 have been amended to recite that the resting freeze-dried platelets can form a clot when contacted with thrombin for 3 minutes at 37° C. This recitation is supported throughout the specification, including original claim 13 and page 4, lines 6-8. Although the objected to phrase did not appear in claim 26, to expedite prosecution, claim 26 has also been amended to contain a parallel recitation.

The amendments are believed to obviate the rejection. Reconsideration and withdrawal of the rejection are respectfully requested.

#### **C. Rejection of the Claims as Anticipated**

Claims 1-10 are rejected under §102(b) as anticipated by Roser, U.S. Patent No. 6,221,575 (hereafter, "Roser"). According to the Action, Roser teaches platelets loaded with

trehalose. It asserts that Roser teaches loading the platelets differently, but that "the resultant product would appear to be the same." Action, at page 4. Applicants amend in part and traverse.

Claim 1 has been amended to recite that the loaded platelets of the invention are resting and will clot when exposed to thrombin after freeze-drying and rehydration. The Examiner will appreciate that platelets are generally characterized in the art as being in one of two states: resting (unactivated), and activated. Loading platelets with trehalose to stabilize them during drying without activating them has been a goal in the art for years. Unfortunately, this goal is not reached by Roser.

As explained in the accompanying Declaration of Dr. Fern Tablin, none of the methods taught by Roser provide a means for obtaining resting platelets that are loaded with sufficient trehalose to stabilize the platelets so that they retain biological activity after being freeze-dried and rehydrated. Roser teaches the following with respect to introducing trehalose into platelets:

Suitable methods include, but are not limited to, electroporabilisation, phase transition of the membrane, osmotic methods such as the use of organic osmolytes and pinocytosis, transient lysis methods such as acid shock and reversible cross-linking and the use of membrane permeable, esterase-labile trehalose derivatives. Effective means of electroporabilisation are described for instance in the Examples herein and in Hughes and Crawford (1989), *Biochimica Biophysica Acta* 981:277-287; and Hughes and Crawford (1990) 634th Meeting, Bath, *Biochemical Society Transactions* 871-873. Effective means of phase transition of the membrane for platelet loading with trehalose are described for instance in Oliver et al. The Bethesda Meeting. Effective means of pinocytosis are described for instance in Okada and Rechsteiner (1982) *Cell* 29: 33; and Rechsteiner (1987) *Methods in Enzymology* 149: 42. Effective means of transient lysis are described for instance in Magnani et al. (1992) *Proc. Natl. Acad. Sci.* 89:6477; Ihler and Tsang 1987 *Methods in Enzymology* 149: 221; and Dale (1987) *Methods in Enzymology* 149:229.

Roser, '575 patent, at column 5, lines 17-41.

As Dr. Tablin explains in her Declaration, electroporabilisation activates platelets. Tablin Declaration, at ¶7. It is therefore not suitable as a method for providing a trehalose-loaded, resting platelet.

As Dr. Tablin further explains in her Declaration, transient lysis does not provide a method for obtaining trehalose-loaded, resting platelets that are stabilized enough to maintain clotting functionality after being freeze-dried and rehydrated.

Further, the "pinocytosis" to which Roser refers, however, is not what is commonly thought of as "pinocytosis" but is rather a so-called "osmotic lysis" technique taught in two references by Rechsteiner, in which L929 cells are subjected to osmotic manipulations to introduce macromolecules into cellular cytoplasm. Tablin Declaration, at ¶9. L929 cells are nucleated, murine cells. The cells were first incubated in a hyperosmotic, 0.5 M sucrose solution, which shrank the volume of the cell cytoplasm, and then subjected to a hypotonic culture medium, which caused the cytoplasm of the cells to expand. According to the references, any pinosomes that had entered the cytoplasm from the hypertonic solution then burst due to the osmotic difference, and released their contents. Tablin Declaration, at ¶10.

Nucleated mammalian cells, such as the L929 cells used in the Rechsteiner papers, are much larger than platelets and have far more membrane surface. They are therefore much more able to withstand the osmotic manipulations necessary to practice the osmotic lysis method as taught by Rechsteiner. It is Dr. Tablin's opinion, based on almost two decades of experience in working with platelets, that subjecting platelets to the osmotic manipulations taught by Rechsteiner would activate the platelets. Tablin Declaration, at ¶11. One of the two Rechsteiner references referred to in Roser is provided as Attachment 2 to the Tablin Declaration. A copy of the second Rechsteiner reference is being obtained and will be forwarded as soon as it is available.

Finally, Roser also mentions that trehalose can be loaded into platelets by phase transition, and cites as support a presentation by Ann Oliver at a 1996 meeting in Maryland (the so-called "Bethesda Meeting," see, Roser, col. 2, lines 4-8) as support. Ms. Oliver is one of the inventors named on the present application. The phase transition Ms. Oliver was talking about in 1996 was the phase transition that platelets undergo between 12° and 20° C. See, specification, at page 6, lines 21-22. Unfortunately, platelets at this phase transition temperature do not take up enough trehalose to stabilize them during drying. Tablin Declaration, at ¶12.

Thus, Roser does not teach methods that permit loading platelets with sufficient trehalose to stabilize them during freeze-drying and permitting them to be rehydrated and to respond to thrombin by clotting, as recited in the claims. Accordingly, Roser does not anticipate the claims as presented. Reconsideration and withdrawal of the rejection is respectfully requested.

#### **D. Rejection of the claims as obvious**

##### **1. Rejection over Read in view of Roser**

Claims 15-17 and 26-34 are rejected under §103(a) as obvious over Read, U.S. Patent No. 5,902,608 (hereafter, "Read"), in view of Roser, *supra*. According to the Action, Read teaches hemostasis aids including platelets and also therapeutic methods of using platelets, but does not teach loading the platelets with trehalose. The Action asserts that it would have been obvious to substitute the trehalose-loaded platelets of Roser into the compositions and methods of Read because Roser teaches that trehalose loaded platelets are dehydration tolerant. Action, at page 6. Applicants amend in part and traverse.

Substitution of the "trehalose-loaded platelets of Roser" into the compositions and methods of Read would not render obvious the invention as now claimed. The claims now recite use of trehalose loaded resting platelets. As pointed out in the preceding section, Roser does not teach loading trehalose into resting platelets in amounts adequate to stabilize them for freeze-drying, and thus does not teach the invention as now claimed. Accordingly, even if the Roser

platelets were substituted in the Read compositions and methods, it would not provide the invention as claimed, nor how to achieve it.

## **2. Rejection over Gurewich in view of Roser**

Claims 11-14 are rejected under §103(a) as obvious over Gurewich, U.S. Patent No. 5,902,608 (hereafter, "Gurewich"), in view of Roser, *supra*. According to the Action, Gurewich teaches loading platelets with therapeutic agents, but does not teach using trehalose-loaded platelets. The Action asserts that it would have been obvious to substitute the trehalose-loaded platelets of Roser into the compositions and methods of Gurewich because Roser teaches that trehalose loaded platelets are dehydration tolerant. Action, at page 6. Applicants amend in part and traverse.

As previously noted, the invention as now claimed recites the use of resting platelets which have been loaded with trehalose in amounts sufficient so that they retain the ability to clot after being freeze-dried. Substitution of the "trehalose-loaded platelets of Roser" into the compositions and methods of Gurewich would therefore not render obvious the invention as now claimed since Roser does not teach loading trehalose into resting platelets in amounts adequate to stabilize them for freeze-drying, and thus does not teach the invention as now claimed. Accordingly, even if the Roser platelets were substituted in the Read compositions and methods, it would not provide the invention as claimed, nor how to achieve it. As Dr. Tablin notes in her Declaration, resting platelets will last longer in the circulation and are preferred to activated platelets (such as the electroporated platelets of Roser's examples) for infusion into persons in need thereof.

Reconsideration and withdrawal of the rejection is respectfully requested.

## **3. Rejection as obvious over Roser**

Claims 1-10 are rejected under §103(a) as obvious over Roser. According to the Action, Roser teaches platelets loaded with trehalose. The Action states that, even if Roser does not anticipate the invention per se, Roser does suggest the optimal internal concentration of

trehalose and teaches that platelets can be dried and stabilized by loading them with 10 -125 mM trehalose. Applicants amend in part and traverse.

As pointed out above, the invention as now claimed recites the use of resting platelets which have been loaded with trehalose in amounts sufficient so that they retain the ability to clot after being freeze-dried. As set forth in the Tablin Declaration, three of the methods taught by Roser activate platelets from their resting state, and the fourth, the use of the only phase transition known in 1996, does not result in loading platelets with sufficient trehalose to provide adequate stabilization during freeze drying. Accordingly, Roser does not teach or suggest the invention as now claimed, and does not render it obvious.

#### **4. Ownership of the Claims**

The rejection under §103(a) contains a form paragraph noting "the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made" and that Applicants' are obligated to "point out the inventor and invention dates of each claim that was that was not commonly owned at the time a later invention was made." Action, at page 5.

Applicants' counsel recently became aware that one of the inventors may have been under an obligation of assignment to a different employer at the time of the invention. A determination has not yet been made as to whether the invention or inventions embodied in the present claims were made at different times and, thus, whether or not there is a difference in the ownership of the claims. The Examiner will be notified should a determination be made that there are inventions having different ownership within the pending claims.

#### **IV. Information Disclosure Statement**

The Examiner's attention is called to the Information Disclosure Statement (IDS) being submitted regarding this application. Consideration of the references, and return of the form, initialed to show the Examiner's consideration, are respectfully requested.

**V. Correct Correspondence Address and Attorney Docket Number**

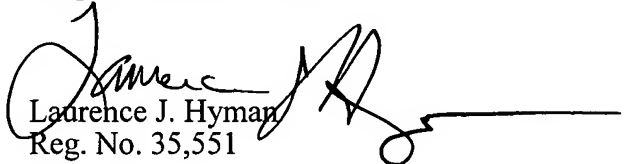
The Office/ Action of June 22, 2005, was incorrectly mailed to the previous attorney for the Applicants and bore the previous counsel's docket number. An appropriate change of correspondence address form was filed with respect to this application on October 12, 2004. Applicants respectfully request the Examiner's assistance in ensuring that future communications regarding this case are mailed to the undersigned attorney. Applicants also ask the Examiner's assistance in having the attorney docket number for this application changed to 023070-149640US.

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

  
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